AHRQ Comparative Effectiveness Review Surveillance Program

CER #33 :
Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults

Original release date:
September 2011

Surveillance Report:
August 2012

Key Findings:

- All conclusions regarding the comparative efficacy and safety of non-pharmacological interventions are still considered valid
- No new significant safety concerns were identified
- Several new studies were identified that suggested that transcranial magnetic stimulation, vagus nerve stimulation and some types of CBT may be effective but sample sizes were small and studies were not controlled

Summary Decision

This CER's priority for updating is **Low**

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Non-pharmacological Interventions for Treatment-Resistant Depression in Adults: An Assessment for the Need to Update the 2011 Evidence Review

1. Introduction

Comparative Effectiveness Review (CER) #33, Nonpharmacological Interventions for Treatment-Resistant Depression in Adults, was released in September 2011.[1] It was therefore due for a surveillance assessment in March, 2012.

2. Methods

2.1 Literature Searches

Using the search strategy employed for the original report, we conducted a limited literature search of Medline for the years 2010-March 20, 2012. Initially, this search included five high-profile general medical interest journals (Annals of Internal Medicine, British Medical Journal, Journal of the American Medical Association, Lancet, and the New England Journal of Medicine) and five specialty journals (American Journal of Psychiatry, Archives of General Psychiatry, Biological Psychiatry, British Journal of Psychiatry, and Journal of Clinical Psychiatry). The specialty journals were those most highly represented among the references for the original report. However, because of the small number of relevant articles this search produced, a subsequent search was run that was not limited to the 10 journals. Appendix A includes the search methodology for this topic.

2.2 Study selection

In general we used the same inclusion and exclusion criteria as the original CER.

2.3 Expert Opinion

We shared the conclusions of the original report with 17 experts in the field (including the original project leader, suggested field experts, original technical expert panel (TEP) members, and peer reviewers) for their assessment of the need to update the report and their recommendations of any relevant new studies; five subject matter experts responded. Appendix C shows the questionnaire matrix that was sent to the experts.

2.4 Check for qualitative and quantitative signals

After abstracting the study conditions and findings for each new included study into an evidence table, we assessed whether the new findings provided a signal according to the Ottawa Method and/or the RAND Method, suggesting the need for an update. The criteria are listed in the table below.[2,3]

	Ottawa Method
	Ottawa Qualitative Criteria for Signals of Potentially Invalidating Changes in Evidence
A1	Opposing findings: A pivotal trial or systematic review (or guidelines) including at least one new trial that characterized the treatment in terms opposite to those used earlier.
A2	Substantial harm: A pivotal trial or systematic review (or guidelines) whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making.
A3	A superior new treatment: A pivotal trial or systematic review (or guidelines) whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.
	Criteria for Signals of Major Changes in Evidence
A4	Important changes in effectiveness short of "opposing findings"
A5	Clinically important expansion of treatment
A6	Clinically important caveat
A7	Opposing findings from discordant meta-analysis or nonpivotal trial
	Quantitative Criteria for Signals of Potentially Invalidating Changes in Evidence
B1	A change in statistical significance (from nonsignificant to significant)
B2	A change in relative effect size of at least 50 percent
	RAND Method Indications for the Need for an Update
1	Original conclusion is still valid and this portion of the original report does not need updating
2	Original conclusion is possibly out of date and this portion of the original report may need updating
3	Original conclusion is probably out of date and this portion of the original report may need updating
4	Original conclusion is out of date

2.5 Compilation of Findings and Conclusions

For this assessment we constructed a summary table that included the key questions, the original conclusions, and the findings of the new literature search, the expert assessments, and any FDA reports that pertained to each key question. To assess the conclusions in terms of the evidence that they might need updating, we used the 4-category scheme described in the table above for the RAND Method.

In making the decision to classify a CER conclusion into one category or another, we used the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still valid.
- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that

might change the conclusion, then we classified the CER conclusion as possibly out of date.
- If we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably out of date.
- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

2.6 Determining Priority for Updating

We used the following two criteria in making our final conclusion for this CER:

- How much of the CER is possibly, probably, or certainly out of date?
- How out of date is that portion of the CER? For example, would the potential changes to the conclusions involve refinement of original estimates or do the potential changes mean some therapies are no longer favored or may not exist? Is the portion of the CER that is probably or certainly out of date an issue of safety (a drug withdrawn from the market, a black box warning) or the availability of a new drug within class (the latter being less of a signal to update than the former)?

3. Results

3.1 Search

The literature search identified 110 titles. After title and abstract review, 82 titles were rejected because they were editorials or letters or did not include topics of interest. The remaining 28 journal articles went on for further review. In addition to the searches, we also reference-mined articles that met inclusion criteria as well as non-systematic reviews identified by the literature searches but found no other articles. Three additional articles were reviewed at the suggestion of the experts.

Thus, through literature searches and expert recommendations, 31 articles went on to full text review. Of these, 22 articles were rejected because they were non-systematic reviews, did not include a comparison of interest, or enrolled patients who had major depression but not treatment-resistant depression. Thus, 9 articles were abstracted into an evidence table (Appendix B).[4-12]

The FDA MedWatch searches identified no notifications of relevance.

3.2 Expert Opinion

The five experts were in general agreement that none of the conclusions changed based on new evidence. Although several suggested new studies, none of the new studies enrolled patients with treatment-resistant depression.

3.3 Identifying qualitative and quantitative signals

Table 1 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, the recommendations of the Southern California Evidence-based Practice Center (SCEPC) regarding the need for update, and qualitative signals.

Table 1: Summary Table

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Key Question 1a: For adults with treatment-resistant depression (TRD, defined as two or more failed adequate trials of a biologic [i.e., pharmacologic] intervention), do non-pharmacologic interventions such as electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), or demonstrated effective psychotherapy (e.g., cognitive therapy[CBT or IPT]) differ in efficacy or effectiveness in treating acute-phase depressive symptoms (e.g., response and remission), whether as a single treatment or part of a combination treatment?				
A very small number of head-to-head trials have shown no differences between ECT and rTMS or ECT and ECT+rTMS for depressive severity, response rates, and remission rates. No trial involved a direct comparison of psychotherapy with another non-pharmacologic intervention.	Two very small new uncontrolled trials report positive effects of rTMS on patients with TRD as assessed by decreases in HDRS.[10,11] One small study of 3 different intensity levels of ECT found no differences in efficacy between the two higher intensities but a lower effect on the BDI score with the lowest intensity[9]	n/a	2/5 experts state conclusion still up-to-date. 2/5 experts cited a RCT (Keshtkar 2011) suggesting ECT might be better than rTMS but sample had MDD, not TRD 1/5 cited Watkins 2011,{#3561} suggesting efficacy of rumination-focused CBT 1/5 did not respond.	Original conclusion is still valid and this portion of the original report does not need updating
Key Question 1b: How do these nonpharmacologic treatments compare with pharmacological treatments in efficacy or effectiveness in treating acute-phase depressive symptoms after two or more failed adequate trials?				
One trial that compared the efficacy of ECT with paroxetine among a mixed MDD/bipolar population showed that ECT produced a significantly greater decrease in depressive severity (9 points by HAM-D) and significantly better response rates (71 percent vs. 28 percent) than paroxetine (low strength of evidence).	One small trial that compared augmentation of pharmacological treatment with HFrTMS to pharmacological treatment alone found symptom reduction with the combination treatment.[4] A second small trial found similar results with aTMS[7] A trial that combined TMS with positive or negative cognitive-emotional reactivation or no behavioral treatment found that no reactivation or positive reactivation were associated with improvement in BDI score but	n/a	3/5 experts state conclusion still up-to-date. 2/5 did not respond.	Original conclusion is still valid and this portion of the original report does not need updating

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
	negative reactivation did not lead to improvement.[8] 1 small study of VNS implants among patients who continued pharmacotherapy found consistent positive effects on BDI and inconsistent improvement on other scales for a portion of patients[5]			
Key Question 2. For adults with TRD, do nonpharmacologic interventions differ in their efficacy or effectiveness for maintaining response or remission (e.g., preventing relapse or recurrence) whether as a single treatment or part of a combination treatment?				
No head-to-head trials compared ECT, rTMS, VNS, or CBT with respect to maintaining remission (or preventing relapse).	One small study found rumination-focused CBT to improve remission better than treatment as usual[12]	n/a	2/5 experts state conclusion still up-to-date 1/5 experts cite two studies (Kuyken 2008; Segal 2010) showing MBCT and medication equivalent for recurrences but patients did not have TRD 1/5 expert said he didn't know 1/5 did not respond.	Original conclusion is still valid and this portion of the original report does not need updating
Key Question 3: Do nonpharmacologic interventions (single or combination) differ in their efficacy or effectiveness for treating TRD as a function of particular symptom subtypes (e.g., catatonic [frozen or hyper] or psychotic symptoms?				
We identified no trials of individuals who fit our definition of treatment-resistant depression that addressed whether procedure-based treatments differed as a function of symptom subtypes. Also, no comparative evidence was available about psychotherapy in subgroups defined by symptom clusters.	One small trial of ultrabrief ECT found no difference in response between patients with unipolar depression and those with bipolar depression[9]	n/a	2/5 experts state conclusion still up-to-date 1/5 experts state that a study of MBCT for TRD is underway but results not reported yet. 1/5 expert said he didn't know. 1/5 did not respond.	Original conclusion is still valid and this portion of the original report does not need updating
Key Question 4. For adults with TRD, do nonpharmacologic interventions differ in their safety, adverse events, or adherence? Adverse effects of interest include but are not				

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
limited to amnesia, memory loss, headaches, and postoperative complications.				
In examining safety, adverse events, and adherence, we found some differences across the interventions in the harms and negative side effects to patients. However, the data were insufficient to reach a conclusive result. *Cognitive functioning*. Some evidence suggests no differences in changes in cognitive functioning between groups, while some evidence suggests ECT may have a deleterious impact on cognitive functioning compared to rTMS (insufficient strength of evidence). *Specific adverse events*. One study comparing ECT with a combination of ECT and rTMS found no differences in specific adverse events (low strength of evidence). *Withdrawals*. We looked at both withdrawals that investigators attributed to adverse events and overall numbers or rates of withdrawals. A single study with a small sample size indicated no difference in withdrawals due to adverse events for the ECT group when compared to rTMS but did not report on the significance of this result (low strength of evidence).	TMS: No new head-to-head studies were identified. Five small studies of TMS identified headache,[8] scalp pain,[4] dizziness,[10] a combination of a foul taste and smell sensation,[11] 1 report of no seizures,[7] 1 case of seizures in a pt. with seizure Hx,[8] and 6 cases of suicidal ideation (in patients with Hx of suicidal ideation).[7,8]None of these studies reported on cognitive functioning. Studies that reported on withdrawals due to AEs found 1 withdrawal due to scalp pain,[4]15 due to intolerance or discomfort, 5 due to suicidal ideation, and 1 due to seizure.[8] ECT: 1 study reported greater impairments in verbal memory in two groups receiving higher-intensity therapy than the 3rd, lower intensity, group. [6] VNS was associated with no serious AEs but commonly with hoarseness, dyspnea, nausea, pain, and anxiety; less frequent were cough, chest tightness, sore throat, dysphagia, and earache.[5]	n/a	4/5 experts state conclusion still up-to-date 1/5 experts provided a nonsystematic but comprehensive review on neurocognitive impacts of neuro-modulation techniques, but main conclusion was that more research is needed (Moreines, 2011).	Original conclusion is still valid and this portion of the original report does not need updating
Key Question 5. How do the efficacy, effectiveness, or harms of treatment with nonpharmacologic treatments for TRD differ for the following subpopulations: elderly, very elderly, and other demographic groups (defined by age, ethnic or racial groups, and sex); and patients with medical comorbidities (e.g., seizure history, stroke, diabetes,				

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
dementia, perinatal depression, ischemic heart disease, cancer)				
We found no studies directly comparing non-pharmacologic interventions in selected populations, such as the elderly, those with stroke, or those with other medical comorbidities. Two trials compared rTMS with sham, one in young adults (ages 18–37) and one in older adults with post-stroke depression. The trial in younger adults found that rTMS decreased depression severity compared with sham. The trial in older adults found that rTMS decreased depression severity but not remission compared with the sham control.	One relatively small study of ECT among elderly with varying degrees of cognitive impairment found that those with no or mild cognitive impairment had improvement in depression symptoms at 6 weeks and 6 months, whereas those with dementia had non-significant improvement only.[6]	n/a	2/5 experts state conclusion still up-to-date 1/5 experts states conclusion still up to date for young adults but doesn't know about elderly 1/5 experts cited a study comparing CBT with pharmacological treatments that concluded that CBT can be comparable to medications but that outcomes depend on level of therapist experience but patients had MDD , not TRD, and already cited as background in original report. 1/5 experts did not respond.	Original conclusion is still valid and this portion of the original report does not need updating
Key Question 6: For adults with TRD, do non-pharmacologic interventions differ in regard to other health-related outcomes (e.g., quality of life)?				
One study found no differences between ECT and ECT+rTMS in performance on the Global Assessment of Functioning scale (low strength of evidence).	One very small study of HFrTMS found increases in QOL scores for global, physical, and psychological domains but not social or environmental.[4]	n/a	2/5 experts state conclusion still up-to-date 1/5 states he doesn't know. 1/5 did not respond.	Original conclusion is still valid and this portion of the original report does not need updating

Are there new data that could inform the key questions that might not be addressed in the conclusions?

2/5 experts stated that there were no new data.

Legend: a rTMS=accelerated repetitive transcranial magnetic stimulation; ECT=electroconvulsive therapy; HFrTMS=high-frequency repetitive transcranial magnetic stimulation; QOL=quality of life; SCEPC Southern California Evidence-based Practice Center; VNS=vagus nerve stimulation

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Appendices

Appendix A: Search Methodology

Appendix B: Evidence Table

Appendix C: Questionnaire Matrix

Appendix A. Search Methodology

Treatment-Resistant Depression CER
update searches (2010 – present)
HQ242-3014
PubMed (3/20/2012)

#23	Add	Search **#11 OR #18 OR #20 OR #22**	110	08:58:20
#22	Add	Search **#7 AND #21**	8	08:56:35
#21	Add	Search **vagus nerve stimulation[mesh] OR "vagus nerve stimulation"[tw]**	1179	08:56:22
#20	Add	Search **#7 AND #19**	59	08:55:20
#19	Add	Search **transcranial magnetic stimulation[mesh] OR "(r)tms"[tw]**	4690	08:54:57
#18	Add	Search **#15 OR #17**	34	08:54:25
#17	Add	Search **#13 AND #16**	22	08:54:11
#16	Add	Search **longitudinal studies[mh] OR comparative study[ptyp] OR cohort studies[mesh] OR "observational studies"[tw]**	2490151	08:53:58
#15	Add	Search **#13 AND #14**	17	08:52:55
#14	Add	Search **randomized controlled trial[ptyp] OR "randomized controlled trials as topic"[mesh] OR "single-blind method"[mesh] OR "random allocation"[mesh]**	453278	08:51:40
#13	Add	Search **#7 AND #12**	82	08:48:20
#12	Add	Search **electroconvulsive therapy[mesh] OR ect[tw] OR "electroconvulsive therapy"[tw]**	11640	08:48:06
#11	Add	Search **#9 AND #10**	13	08:47:25
#10	Add	Search **drug resistance[mesh] OR refractory[tw] OR resistant[tw]**	451700	08:46:16
#9	Add	Search **#7 AND #8**	678	08:45:42
#8	Add	Search **socioenvironmental therapy[mesh] OR "interpersonal psychotherapy"[tw] OR ipt[tw] OR psychotherapy[mesh] OR cognitive therapy[mesh] OR "cognitive behavioral therapy"[tw] OR cbt[tw]**	139250	08:38:52
#7	Add	Search **#2 NOT #6**	8001	08:36:53
#6	Add	Search **#3 OR #5**	1383	08:36:37
#5	Add	Search **#2 AND #4**	838	08:35:58
#4	Add	Search **case control studies[mesh]**	536608	08:35:17
#3	Add	Search **depression[mesh] OR depressive disorder[mesh]** Limits: **Humans, Editorial, Letter, Case Reports, English, All Adult: 19+ years, Young Adult: 19-24 years, Adult: 19-44 years, Middle Aged: 45-64 years, Middle Aged + Aged: 45+ years, Aged: 65+ years, 80 and over: 80+ years, Publication Date from 2010**	557	08:34:23
#2	Add	Search **depression[mesh] OR depressive disorder[mesh]** Limits: **Humans, English, All Adult: 19+ years, Young Adult: 19-24 years, Adult: 19-44 years, Middle Aged: 45-64 years, Middle Aged + Aged: 45+ years, Aged: 65+ years, 80 and over: 80+ years, Publication Date from 2010**	9384	08:34:07
#1	Add	Search **depression[mesh] OR depressive disorder[mesh]**	131392	08:32:37

Appendix B. Evidence Table

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions (and outcomes measures)	Findings
Key Question 1a: Efficacy of Nonpharmacologic Interventions Against Other Nonpharmacologic Interventions				
TMS				
Rosenberg, 2010[11] Efficacy of deep TMS in MDD pts who have demonstrated resistance to ECT	Inclusion:DSM-IV MDD with drug resistance and non-response to ECT.	6 pts. w/ mean HDRS of 31, mean HARS of 25	HDRS-24 SCID BDI HARS Response defined as reduction in HDRS of at least 50%; remission was defined as a reduction to <10.	All pts. completed 10 tx. 2 dropped out after the 10th tx, 1 due to suicidal ideation and 1 due to non-response. Mean HDRS decreased to 17. Four pts. completed 15 tx.w/ mean HDRS of 16.8. 2 additional pts dropped out after 15 sessions. Remaining 2 pts completed 20 tx: one attained remission, and the 2nd attained response
Rosenberg, 2011[10] Efficacy of a 2nd tx with deep TMS in pts who responded to a first tx but then relapsed	Inclusion: DSM-IV MDD with drug resistance, who previously responded to deep TMS tx	8 pts. mean age 47. During each tx episode, 4 of the patients were antidepressant – free (not the same 4 each time).	HDRS HARS BDI	During the first tx, mean HDRS, HARS, and BDI improved significantly. After the 2nd tx, these 3 outcomes also showed significant improvement cf. baseline; however, improvement was not as great as w/ the initial course of tx (64.1% vs. 50.7% for the HDRS; 59.7% v. 47.5% for the HARS, and 67.7% vs. 25.8% for the BDI)
ECT				
Quante, 2011[9] Comparative efficacy of 3 different ultrabrief ECT stimulus intensities (pilot RCT)	Inclusion: TRD (DSM-IV MD or BPD [9]) Exclusion: Coarse brain disease, ECT within 6 mos of study, substance abuse, and pulmonary disease.	41 inpatients (23.2% male) in German hospital, ages 18-85 (mean age 56.5±13.9), all on antidepressants	HDRS-28 MADRS YMRS BDI VLMT Wechsler Memory Scale	Response rate across arms was 43.8%. No differences were seen by intensity except for BDI, where the lowest intensity was not associated with a reduction in score.

			Regensburger Wortflüssigkeits-Test Primary outcome was reduction in HDRS, BDI, response rate of 50%	No differences were seen in neuropsych tests (VLMT) except for impairments in verbal memory in the two higher-intensity groups
Key Question 1b: Efficacy of Nonpharmacologic Interventions Compared With Antidepressant Pharmacotherapies				
TMS				
Berlim, 2011[4] Pre-post comparison of patients treated with HF rTMS as augmenting strategy for pharmacological treatment	Inclusion: Primary dx current MDD (SCID-I and HAM-D_{24}), std. definition TRD, stable dose antidepressant for prior 4 weeks and duration of trial Exclusion: current psychotic features, lifetime hx any non-mood psychiatric disorder; lifetime hx bipolar disorder I or II, current substance and/or alcohol abuse/dependence within prior 6 months, current neurological disease, pregnancy , use of any ECT within current MDE; any contraindication for rTMS (e.g., personal hx epilepsy, metallic head implants)	15 participants (7 males) seen at 1 academic center in Canada; mean age 47 (33-61), 14/15 Caucasian; 73.4% recurrent MDD; 73.4% comorbid Axis II disorders	HAM-D_{24} IDM-SR_{30} HAM-A BAI CGI-S WHO QOLBREF (quality of life)	All clinical scales, both clinician- and self-reported (anxiety and depression), showed symptom reduction at 4 weeks (limits: small sample size and non-controlled design)
Holtzheimer, 2010[7] Pre-post comparison of patients treated with accelerated TMS (aTMS) in addition to their pharmacological tx	Inclusion: (1) a current major depressive episode; (2) 24-item Hamilton Depression Rating Scale (HDRS24)≥20 at screening; (3) ≤3 adequate medication failures in the current episode; (4) willingness to remain on current psychotropic medications with unchanged doses for at least 2 weeks before and 6 weeks following	14 participants (9 male) recruited through physician referral in academic medical center in GA. Median age 51 (20-74); 13 Caucasian/1 Black; 1 had BPD 2; median current episode duration 9 mos. (3-96 mos). 2 patients failed to complete tx and 36% failed to complete all study visits.	aTMS consisted of 15 sessions over 2 days. Assessment at baseline, after treatments, and 3- and 6 weeks. Assessments included HDRS24, HRSA, BDI-2, and RBANS. Response was defined as ≥50% decrease in HDRS24 score from baseline. Remission was defined as HDRS24 score ≤10.	Depression and anxiety decreased significantly after tx. Response rates were 43, 36, and 36%, respectively. Improvements persisted at 3 and 6 weeks

	treatment; (5) no prior exposure to TMS or rTMS; (6) no clinically significant psychiatric or medical comorbidities; and (7) no increased risk of seizure (e.g., prior seizure, brain tumor, or concomitant medications that lower seizure threshold [such as bupropion])			
TMS plus cognitive emotional reactivation				
Isserles, 2011[8] Assessment of deep TMS with or without positive or negative cognitive-emotional reactivation (guided mood alterations) as an adjunctive tx to antidepressants	Inclusion: A diagnosis of non-psychotic MDD with HDRS-24N21 and treatment failure with at least two antidepressant medications, right handedness, no other DSM-IV axis I or major axis II disorder and absence of known TMS risk factors	57 adults recruited through newspaper and radio ads to two Israeli medical centers. 46 completed at least 2 weeks of the study. Only 20 completed weekly tx. Mean age for the 46: ~ 43, ~50% male; Mean length of current episode was 25 months in the negative and no cognitive tx groups and 54 mos in the positive group.	Primary outcome measure: HDRS-24 at the end of the 4-week daily tx phase. MD defined as HDRS-24 score of ≥22. Response was defined as an improvement of 50% or more. And remission as an HDRS-24 of ≤10 Secondary outcome: cognitive assessment with Mindstreams	Deep TMS without reactivation or with positive reactivation was associated with improvement or remission. The group that received negative reactivation did not have significant response (smaller improvements in HDRS-24 and no improvements in BDI scores). Positive response was predicted by stimulus intensity. (limitations included lack of controls)
VNS				
Cristancho, 2011[5] Pre-post comparison of pts. treated with VNS on top of their usual pharmacological tx	Inclusion: DSM-IV dx MDD or BPD and currently in a MDE (based on clinical judgment) Exclusion: Implants received at another institution; primary dx other than MDD or BPD, psychotic features in current episode	15 participants who received VNS implants of whom 13 completed 1 year FU (6 males), mean age 49; all Caucasian; mean length of current episode 63.8 months	Primary: Response: BDI decrease @ 6, 12 mos. From baseline (1st visit after implantation) of at least 50% Remission: score of ≤9@ 12 mos. Secondary: Categorical outcomes (response and remission rates) on the BDI and changes in the HDRS-17, HDRS-24, CGI-I, BAI, BHS, Q-LES-Q,	13 pts completed 1 yr. Mean 12-mo. BDI was 35% decreased, significant difference (difference also significant at 6 mos.). Other scales showed improvement or remission for a portion of patients.

			# hospitalizations and suicide attempts in the 12-month FU	
Watkins, 2011[12] RCT of 12-session rumination-focused CBT vs. treatment as usual (pharmacological treatment and outpatient clinical mgt.)	Inclusion: Age <18, meeting criteria for medication-refractory residual depression as defined previously: (a) meeting DSM-IV criteria for major depression within the past 18 months but not in the past 2 months; (b) residual symptoms reaching at least 8 on the 17-item HRSD and 9 on the BDI-II (c) taking antidepressant medication at a therapeutic dose as recommended by the British National Formulary and/or equivalent to 125 mg of amitriptyline for at least 8 weeks continuously during the current episode and within the past 2 months Exclusion: History of bipolar disorder, psychosis, current drug or alcohol dependence, intellectual disability, organic brain damage and concurrent psychotherapy at point of entry to the study	42 consecutively recruited individuals in two UK locations	Severity of residual depressive symptoms Primary: HRSD (response defined as ≥50% decrease in baseline HRSD) BDI Secondary: SCID RRS (change from T1 to T2 in self-reported rumination, number of comorbid psychiatric diagnoses, and number of individuals meeting criteria for remission (HRSA≤8 and BDI<9 at termination) and relapse (defined as a participant meeting DSM-IV criteria for a new episode of MD at any point between T1 and T2)	Rumination focused CBT was associated with significantly fewer residual depressive symptoms post intervention cf. the TAU group. The intervention was also associated with significantly less depressive rumination, greater treatment response and remission, decreased relapse and comorbid axis II diagnoses, and a trend toward fewer comorbid axis I disorders
Key Question 2: Maintenance of Remission or Prevention of Relapse				
Watkins, 2011[12] RCT of 12-session rumination-focused CBT vs. treatment as usual (pharmacological treatment and outpatient clinical mgt.)	See above			Rumination focused CBT was associated with greater remission and decreased relapse

Key Question 3: Efficacy of Nonpharmacologic Interventions for Patients With Different Symptomatology				
Quante, 2011[9]	Inclusion: TRD (DSM-IV MD or BPD [9]) Exclusion: Coarse brain disease, ECT within 6 mos of study, substance abuse, and pulmonary disease.	41 inpatients (23.2% male) in German hospital, ages 18-85 (mean age 56.5±13.9), all on antidepressants	HDRS-28 MADRS YMRS BDI VLMT Wechsler Memory Scale Regensburger Wortflüssigkeits-Test Primary outcome was reduction in HDRS, BDI, response rate of 50%	No difference was seen in response rate (to high dose ultrabrief right unilateral ECT) between pts with unipolar depression and those w/BPD
Key Question 4: Safety, Adverse Events, and Adherence				
TMS				
Berlim, 2011[4] Pre-post comparison of patients treated with HF rTMS as augmenting strategy for pharmacological treatment	Inclusion: Primary dx current MDD (SCID-I and HAM-D_{24}), std. definition TRD, stable dose antidepressant for prior 4 weeks and duration of trial Exclusion: current psychotic features, lifetime hx any non-mood psychiatric disorder; lifetime hx bipolar disorder I or II, current substance and/or alcohol abuse/dependence within prior 6 months, current neurological disease, pregnancy , use of any ECT within current MDE; any contraindication for rTMS (e.g., personal hx epilepsy, metallic head implants)	15 participants (7 males) seen at 1 academic center in Canada; mean age 47 (33-61), 14/15 Caucasian; 73.4% recurrent MDD; 73.4% comorbid Axis II disorders	HAM-D_{24} IDM-SR_{30} HAM-A BAI CGI-S WHO QOLBREF (quality of life)	1 of 15 pts withdrew due to severe scalp pain
Holtzheimer, 2010[7] Pre-post comparison of patients treated with accelerated TMS (aTMS) in addition to their	Inclusion: (1) a current major depressive episode; (2) 24-item Hamilton Depression Rating Scale (HDRS24)≥20 at screening; (3) ≤3 adequate	14 participants (9 male) recruited through physician referral in academic medical center in GA. Median age 51 (20-74); 13 Caucasian/1	aTMS consisted of 15 sessions over 2 days. Assessment at baseline, after treatments, and 3- and 6 weeks.	aTMS resulted in no seizure activity, and only 1 pt had a SAE: suicidal ideation

pharmacological tx	medication failures in the current episode; (4) willingness to remain on current psychotropic medications with unchanged doses for at least 2 weeks before and 6 weeks following treatment; (5) no prior exposure to TMS or rTMS; (6) no clinically significant psychiatric or medical comorbidities; and (7) no increased risk of seizure (e.g., prior seizure, brain tumor, or concomitant medications that lower seizure threshold [such as bupropion])	Black; 1 had BPD 2; median current episode duration 9 mos. (3-96 mos). 2 patients failed to complete tx and 36% failed to complete all study visits.	Assessments included HDRS24, HRSA, BDI-2, and RBANS. Response was defined as ≥50% decrease in HDRS24 score from baseline. Remission was defined as HDRS24 score ≤10.	
Isserles, 2011[8] Assessment of deep TMS with or without positive or negative cognitive-emotional reactivation (guided mood alterations) as an adjunctive tx to antidepressants	Inclusion: A diagnosis of non-psychotic MDD with HDRS-24N21 and treatment failure with at least two antidepressant medications, right handedness, no other DSM-IV axis I or major axis II disorder and absence of known TMS risk factors	57 adults recruited through newspaper and radio ads to two Israeli medical centers. 46 completed at least 2 weeks of the study. Only 20 completed weekly tx. Mean age for the 46: ~ 43, ~50% male; Mean length of current episode was 25 months in the negative and no cognitive tx groups and 54 mos in the positive group.	Primary outcome measure: HDRS-24 at the end of the 4-week daily tx phase. MD defined as HDRS-24 score of ≥22. Response was defined as an improvement of 50% or more. And remission as an HDRS-24 of ≤10 Secondary outcome: cognitive assessment with Mindstreams	Deep TMS was associated with a few mild headaches during the 1st week. 15 patients withdrew during daily treatment due to intolerance or tx discomfort. Five pts were withdrawn due to suicidal ideation (these pts had hx of suicidal ideation). One pt., who was on high doses of 3 different antidepressants, had a seizure and was withdrawn. No exacerbations were seen.
Rosenberg, 2010[11] Efficacy of deep TMS in MDD pts who have demonstrated resistance to ECT	Inclusion:DSM-IV MDD with drug resistance and non-response to ECT.	6 pts. w/ mean HDRS of 31, mean HARS of 25	HDRS-24 SCID BDI HARS Response defined as reduction in HDRS of at least 50%; remission was defined as a reduction to <10.	Deep TMS associated with 3 side effects in 1 pt.: foul smell after 5 sessions (disappeared after 19th tx), a bad taste that appeared after 15th tx and also disappeared after 19th tx, and a repulsive smell brought on by specific materials that started after the

				19th tx and continued 40 days after tx cessation
Rosenberg, 2011[10] Efficacy of a 2nd tx with deep TMS in pts who responded to a first tx but then relapsed	Inclusion: DSM-IV MDD with drug resistance, who previously responded to deep TMS tx	8 pts. mean age 47. During each tx episode, 4 of the patients were antidepressant – free (not the same 4 each time).	HDRS HARS BDI	Deep TMS: 1 of 8 pts reported dizziness during the 1st course of tx during the last 10 sessions, suggesting possible tolerance
VNS				
Cristancho, 2011[5] Pre-post comparison of pts. treated with VNS on top of their usual pharmacological tx	Inclusion: DSM-IV dx MDD or BPD and currently in a MDE (based on clinical judgment) Exclusion: Implants received at another institution; primary dx other than MDD or BPD, psychotic features in current episode	15 participants who received VNS implants of whom 13 completed 1 year FU (6 males), mean age 49; all Caucasian; mean length of current episode 63.8 months	Primary: Response: BDI decrease @ 6, 12 mos. From baseline (1st visit after implantation) of at least 50% Remission: score of ≤9@ 12 mos. Secondary: Categorical outcomes (response and remission rates) on the BDI and changes in the HDRS-17, HDRS-24, CGI-I, BAI, BHS, Q-LES-Q, # hospitalizations and suicide attempts in the 12-month FU; Adverse events	No serious adverse events related to VNS. Most frequently reported AEs included hoarseness, dyspnea, nausea, pain, and anxiety; less frequent were cough, chest tightness, sore throat, dysphagia, and earache.
Key Question 5: Efficacy or Harms of Nonpharmacologic Treatments for Selected Patient Subgroups				
Cristancho, 2011[5] Pre-post comparison of pts. treated with VNS on top of their usual pharmacological tx	Inclusion: DSM-IV dx MDD or BPD and currently in a MDE (based on clinical judgment) Exclusion: Implants received at another institution; primary dx other than MDD or BPD, psychotic features in current episode	15 participants who received VNS implants of whom 13 completed 1 year FU (6 males), mean age 49; all Caucasian; mean length of current episode 63.8 months	Primary: Response: BDI decrease @ 6, 12 mos. From baseline (1st visit after implantation) of at least 50% Remission: score of ≤9@ 12 mos. Secondary: Categorical outcomes (response and remission rates) on the BDI and changes in the HDRS-17, HDRS-24, CGI-I, BAI, BHS, Q-LES-Q, # hospitalizations and suicide	None of the tested predictors was found to affect response to VNS except a small assn was found for successful response to ECT in the current MDE

			attempts in the 12-month FU	
Hausner, 2011[6] Efficacy and safety of ECT for elderly with coexisting mild cognitive impairment or dementia	Inclusion: ICD-10 criteria for MDD, TRD or delusional depression	44 elderly German inpatients ≥ 65 (mean 73±6) consecutively enrolled; 24 pts had MRI abnormalities consistent with dementia (10 of 12 w/ dementia had MRI pathologies); withdrawal from all psychotropic meds (except benzodiazepines) 5 days before 1st ECT	MMSE: cognitive performance HDRS-21 Complete remission defined as HDRS≤7	Patients were classified as having no cognitive impairment, mild cognitive impairment, or dementia; after mild transient cognitive decline, the NCI group improved cognitively at 6 wks and 6 mos after ECT. The MCI group improved at 6 mos. The dementia group improved slightly but not significantly (pts being treated for dementia improved while those not being treated deteriorated. ECT resulted in remission of affective symptoms in all 3 groups.
Key Question 6: Health-Related Outcomes of Nonpharmacologic Treatments				
Berlim, 2011[4] Pre-post comparison of patients treated with HF rTMS as augmenting strategy for pharmacological treatment	Inclusion: Primary dx current MDD (SCID-I and HAM-D_{24}), std. definition TRD, stable dose antidepressant for prior 4 weeks and duration of trial Exclusion: current psychotic features, lifetime hx any non-mood psychiatric disorder; lifetime hx bipolar disorder I or II, current substance and/or alcohol abuse/dependence within prior 6 months, current neurological disease, pregnancy , use of any ECT within current MDE; any contraindication for rTMS (e.g., personal hx epilepsy, metallic head implants)	15 participants (7 males) seen at 1 academic center in Canada; mean age 47 (33-61), 14/15 Caucasian; 73.4% recurrent MDD; 73.4% comorbid Axis II disorders	WHO QOLBREF (quality of life)	QOL scores increased significantly for global, physical, and psychological domains but not social or environmental

Table Notes: BAI Beck Anxiety Inventory; BDI Beck Depression Inventory; dx diagnosis; BHS Beck Hopelessness Scale; CGI-I Clinical Global Impressions-Improvement scale; CGI-S Clinical Global Impression – Severity subscale; ECT electroconvulsive therapy; HAM-A Hamilton Anxiety Rating Scale; HAM-D24 (or HDRS24): 24-item Hamilton Depression Rating Scale; HDRS-17 17-item Hamilton Depression Rating Scale; HF rTMS high frequency repetitive transcranial magnetic stimulation; hx history; IDM-SR_{30} 30-item Inventory of Depressive Symptomatology; MADRS Montgomery and Asberg Rating Scale; MDD major depressive disorder; MDE major depression episode; Q-LES-Q Quality of Life enjoyment and Satisfaction Questionnaire; RBANS Repeatable Battery for the Assessment of Neuropsychological Status; RRS Ruminative Response Scale of the Response Styles Questionnaure; SCID-I Structured Clinical Interview for DSM-IV Axis I Disorders; VLMT Verbal Learning Recognition and Memory Test; VNS vagus nerve stimulation; YMRS Young Mania Rating Scale

Appendix C. Questionnaire Matrix

Surveillance and Identification of Triggers for Updating Systematic Reviews for the EHC Program

Title: ***Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults***

Your Name: _____

Your Contact Information (for honorarium): _____

Conclusions From CER Executive Summary	**Is this conclusion almost certainly still supported by the evidence?**	**Has there been new evidence that may change this conclusion?**	**Do Not Know**
Key Question 1a: For adults with treatment-resistant depression (TRD, defined as two or more failed adequate trials of a biologic [i.e., pharmacologic] intervention), do nonpharmacologic interventions such as electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), or demonstrated effective psychotherapy (e.g., cognitive therapy[CBT or IPT]) differ in efficacy or effectiveness in treating acute-phase depressive symptoms (e.g., response and remission), whether as a single treatment or part of a combination treatment?			
A very small number of head-to-head trials have shown no differences between ECT and rTMS or ECT and ECT+rTMS for depressive severity, response rates, and remission rates. No trial involved a direct comparison of	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
psychotherapy with another nonpharmacologic intervention.			
Key Question 1b: How do these nonpharmacologic treatments compare with pharmacological treatments in efficacy or effectiveness in treating acute-phase depressive symptoms after two or more failed adequate trials?			
One trial that compared the efficacy of ECT with paroxetine among a mixed MDD/bipolar population ECT showed that ECT produced a significantly greater decrease in depressive severity (9 points by HAM-D) and significantly better response rates (71 percent vs. 28 percent) than paroxetine (low strength of evidence).	☐	New Evidence:	☐
Key Question 2: For adults with TRD, do nonpharmacologic interventions differ in their efficacy or effectiveness for maintaining response or remission (e.g., preventing relapse or recurrence) whether as a single treatment or part of a combination treatment?			
No head-to-head trials compared ECT, rTMS, VNS, or CBT with respect to maintaining remission (or preventing relapse).	☐	New Evidence:	☐
Key Question 3: Do nonpharmacologic interventions (single or combination) differ in their efficacy or effectiveness for treating TRD as a function of particular symptom subtypes (e.g., catatonic [frozen or hyper] or psychotic symptoms?			

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
We identified no trials of individuals who fit our definition of treatment-resistant depression that addressed whether procedure-based treatments differed as a function of symptom subtypes. Also, no comparative evidence was available about psychotherapy in subgroups defined by symptom clusters.	☐	New Evidence:	☐
Key Question 4: For adults with TRD, do nonpharmacologic interventions differ in their safety, adverse events, or adherence? Adverse effects of interest include but are not limited to amnesia, memory loss, headaches, and postoperative complications.			
In examining safety, adverse events, and adherence, we found some differences across the interventions in the harms and negative side effects to patients. However, the data were insufficient to reach a conclusive result. *Cognitive functioning*. Some evidence suggests no differences in changes in cognitive functioning between groups, while some evidence suggests ECT may have a deleterious impact on cognitive functioning compared to rTMS (insufficient strength of evidence). *Specific adverse events*. One study comparing ECT with a combination of ECT and rTMS found no differences in specific	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
adverse events (low strength of evidence). *Withdrawals*. We looked at both withdrawals that investigators attributed to adverse events and overall numbers or rates of withdrawals. A single study with a small sample size indicated no difference in withdrawals due to adverse events for the ECT group when compared to rTMS but did not report on the significance of this result (low strength of evidence).			
Key Question 5: How do the efficacy, effectiveness, or harms of treatment with nonpharmacologic treatments for TRD differ for the following subpopulations: elderly, very elderly, and other demographic groups (defined by age, ethnic or racial groups, and sex); and patients with medical comorbidities (e.g., seizure history, stroke, diabetes, dementia, perinatal depression, ischemic heart disease, cancer)			
We found no studies directly comparing nonpharmacologic interventions in selected populations, such as the elderly, those with stroke, or those with other medical comorbidities.	☐	New Evidence:	☐
Two trials compared rTMS with sham, one in young adults (ages 18–37) and one in older adults with post-stroke depression. The trial in younger adults found that rTMS decreased depression severity compared with sham. The trial in older adults found that rTMS decreased depression severity but not remission compared with the sham control.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question 6: For adults with TRD, do nonpharmacologic interventions differ in regard to other health-related outcomes (e.g., quality of life)?			
One study found no differences between ECT and ECT+rTMS in performance on the Global Assessment of Functioning scale (low strength of evidence).			
Key Question 6: Health-Related Outcomes of Nonpharmacologic Treatments			
Direct evidence. With respect to patient-reported health-related outcomes, we focused on quality of life (various measures) and ability to function in daily life. One Tier 1 study compared ECT with a combination of ECT and rTMS and found no differences between groups in improvement on the Global Assessment of Functioning scale (low strength of evidence).	☐	New Evidence:	☐
Indirect evidence. Two trials (both in mixed MDD/bipolar populations) assessed general health status and mental and physical functioning (all health domains related to quality of life). In one fair trial, low rTMS had significantly greater improvement in health status and daily	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
functioning than sham, while this relationship approached statistical significance when comparing high rTMS to sham (as measured by the Global Assessment of Functioning scale; low strength of evidence). In the other fair trial, VNS and sham groups did not differ significantly in daily functioning (as measured by the 36-item Medical Outcomes Study Short Form [MOS SF-36]; low strength of evidence). No studies of psychotherapy were identified.			
Are there new data that could inform the key questions that might not be addressed in the conclusions?			